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(54) Title: MULTI-PHASIC DELIVERY VIA TRANSMUCOSAL ABSORPTION OF APPETITE SUPPRESSANTS AND CRAVING REDUCTION MEDICAMENTS

(57) Abstract: The present invention concerns a composition for oral administration of an active for appetite suppression. The composition comprises a carrier, an active or medicament for appetite suppression, and a buffer. The carrier may be a gum, a lozenge, a candy or a tablet suitable for administration in an oral cavity. The buffer is water-soluble, and facilitates bi-phasic release of the active for transmucosal absorption. The method of delivering the active for appetite suppression in a bi-phasic manner is also provided.

# Multi-Phasic Delivery Via Transmucosal Absorption of Appetite Suppressants and Craving Reduction Medicaments

## CROSS REFERENCE TO RELATED APPLICATION AND CLAIM TO PRIORITY

This application is based on provisional application Serial No. 60/376,222, filed April 30, 2002, by John M. Pinney et al. for the invention entitled Multi-phasic Delivery Via Transmucosal Absorption of Appetite Suppressants and Craving Reduction Medicaments, the disclosure of which is incorporated herein by reference, and to which priority is claimed.

## FIELD OF THE INVENTION

The present invention concerns a composition for oral administration of an active for appetite suppression. The composition comprises a carrier, an active or medicament for appetite suppression, and a buffer. The carrier may be a gum, a lozenge, a candy or a tablet suitable for administration in an oral cavity. The buffer is water-soluble, and facilitates bi-phasic release of the active for transmucosal absorption. A method of delivering the active for appetite suppression in a bi-phasic manner is also provided.

## BACKGROUND OF THE INVENTION

Delivery systems containing medicaments, or actives, for oral administration are sometimes administered through a carrier, such as a chewing gum matrix, a lozenge, a tablet or a candy. Formulations permit release of the active over time as the product is masticated or manipulated in the mouth. The action of saliva further facilitates release of

the active, which may then be absorbed by the mucous membranes lining the mouth, throat, larynx and esophagus.

A problem with many delivery system formulations is that they fail to deliver an adequate dosage of active in the appropriate manner over the entire dosing interval. This results in insufficient active being absorbed into the bloodstream for effective therapeutic or pharmacological actions. There are many reasons for inadequate dosing. Many formulations release the active slowly over time in a more or less continuous fashion. Other formulations may retain a significant portion of the active during the prescribed dosing period, resulting in inadequate dosing of the patient. Further, the carrier chosen to contain and subsequently release the active may not perform optimally. For example, a gum prepared from a gum base may be difficult to chew or be unusually hard, thereby damaging the teeth and gums. It has proven quite elusive to find the right qualitative and quantitative parameters for both actives and non-actives comprising the delivery system formulation that will ensure a reliable release rate of the active.

Some delivery formulations have not proven efficacious because they are not properly pH regulated. We have found it necessary to generate a particular pH, and specifically a relatively alkaline pH in the mouth, to allow for the proper release and absorption of many types of actives, i.e., drugs containing a basic nitrogen moiety in their chemical structure. Formulating the appropriate chemistry that will not only generate the proper pH, but do so over the entire release period and do so without overwhelming the patient has proven to be difficult.

As a result of the foregoing problems, many delivery systems provide relatively ineffective active release profiles. For example, conventional delivery systems for

medications relating to appetite suppression and food craving reduction do not provide optimal release profiles.

The amount of active absorbed is partially related to the chewing or manipulation rate of the gum or lozenge, and the time the saliva is held in the mouth. However, these variables are significant only at the extremes of rapid versus slow manipulation, and frequent versus infrequent swallowing. Outside of such extremes, these variables have relatively little impact on active absorption. For example, it generally takes approximately 10 to 30 minutes to achieve adequate blood levels of an active for appetite suppression, regardless of how a user chews or manipulates the carrier. A delay of 10 minutes or more in the release and absorption of the active, however, may be excessively long for someone who is trying to reduce food cravings. Thus, a product that delivers the appetite suppressant active too slowly may be ineffective. Many products simply fail to deliver an adequate dosing of the medication within a few minutes of administration.

There is a need for a delivery system for oral administration of an appetite suppressant active which is highly efficacious in releasing a specified, effective quantity of active shortly after administration, followed by a slower sustained release over an extended period thereafter. The final product should be easy to administer and have highly suitable organoleptic properties that enhance its use. The product should also contain a demonstrably reliable buffer system for maintaining a proper pH inside the mouth to permit optimal absorption of the active.

## SUMMARY OF THE INVENTION

The present invention relates to gums, lozenges, candies, and tablets; and more particularly, to chewing gum, lozenge, candy and tablet compositions that contain orally administered medications that are released in the oral cavity for appetite suppression and food craving reductions. The medications, or actives, contained in the gums, lozenges, and candies can be delivered in a multi-phase release mode. The compositions also contain buffer systems that facilitate oral absorption. A rapid initial release is followed by slower release of medicament, thus creating a bi-phasic release. The initial release counters a craving, while the sustained release prevents further occurrence of the craving.

The buffer system is released simultaneously with the medicament, thereby facilitating transmucosal and buccal absorption of the active(s). As a result, a substantial portion of medication is absorbed quickly, followed by a slower absorption period, thereby enhancing and prolonging delivery of desired ingredients to the bloodstream. The invention thus delivers, first, rapidly an initial pharmacologically effective dose of medicine and, second, a prolonged pharmacologically sufficient dose for longer-term relief of symptoms.

A composition for oral administration of an active for appetite suppression comprises a carrier, an active or medicament for appetite suppression, and a buffer. The carrier may be a gum, a lozenge, a candy or a tablet suitable for administration in an oral cavity. The buffer is water-soluble, and facilitates bi-phasic release of the active for transmucosal absorption.

A method of delivering a medicament for appetite suppression in a bi-phasic manner is also provided. A carrier suitable for oral administration is provided having an active for appetite suppression, as well as a buffer. A first, rapid pharmacologically

effective dose of the active is released in an oral cavity for a first period of time. A second, prolonged pharmacologically sufficient dose of the active is thereafter released in the oral cavity for a second period of time longer than the first period of time.

## DESCRIPTION OF THE FIGURES

Figure 1 is a graph showing a bi-phasic release of an active over a period of time according to an exemplary embodiment of the present invention.

## DETAILED DESCRIPTION OF THE INVENTION

A transmucosal delivery system composition comprises a carrier suitable for oral administration. The carrier is preferably one of a chewing gum, lozenge, candy, and tablet, all of which are suitable for oral administration to a human.

A buffer is dispersed within the carrier. There is sufficient buffer to achieve a predetermined pH within the oral cavity of a user. A suitable buffer for basic active ingredients is potassium carbonate, although calcium and sodium based buffers may also be used. Preferably the buffer and the active are uniformly distributed within the carrier.

An active is also dispersed within the carrier, at least a portion of the active being unionized at the predetermined pH for transmucosal absorption within the oral cavity. In a preferred embodiment, the active is a medicament for appetite suppression, preferably selected from the group of central nervous system stimulants including d-amphetamine, l-amphetamine, mixtures of d- and l-amphetamine, ephedrine, pseudoephedrine, d-methamphetamine, l-methamphetamine, mixtures of d- and l-methamphetamine, phenylpropanolamine, propylhexadrine, related phenylethylamine derivatives,

phentermine, phendimetrazine, and sibutramine. It should be understood that other actives may be provided for relief from other symptoms, cravings, conditions, or provide like therapeutic effect.

The composition of the present invention is a multi-phasic delivery system for medicament in gums, lozenges, candies, and tablets, and a method for making those delivery systems. The delivery is multi-phasic because the active is delivered at different dosing rates, via different forms of the active ingredient, or other than at a constant rate. Via these gums, lozenges, candies, and tablets the invention thus delivers, first, rapidly an initial pharmacologically effective dose of medicine over a relatively short period of time and, second, a pharmacologically sufficient sustained dose for longer-term relief of symptoms, conditions or provision of therapeutic effect over a sustained period of time.

An exemplary embodiment of the release profile of the delivery system of the present invention is best shown in Figure 1. The percentage by weight of active released of the total active in the composition is compared to time. A first, rapid dose D1 of active is released within a predetermined period of time. The predetermined time within which the first dose D1 is provided may vary. Likewise, the amount of active released in the first dose D1 may also vary as desired. Thus, the rate of release of active may vary. A second, sustained dose D2 is thereafter provided, which releases the remaining active over a desired period of time. The period of time over which the second dose D2 is provided may also vary. Furthermore, the percentage by weight of active released of the total active in the composition may also vary.

A detailed description of a two-stage release profile is provided in U.S. Patent No. 6,344,222, the disclosure of which is incorporated herein by reference. The primary

route for delivery of the active is by the transmucosal route (sublingual, buccal, pharyngeal), although some minor amounts of active may be ingested during manipulation of the carrier (for example, chewing gum or sucking and wetting lozenges).

The disclosed delivery system delivers the medicament into the oral cavity for subsequent absorption into the bloodstream in a highly efficacious manner. The speed of release of active ingredients is particularly important because a slow release rate would result in an insufficient amount being absorbed into the bloodstream for relief of symptoms, conditions or cravings, whereas an extremely rapid release rate could result in unpleasant tastes and potential undesirable side effects from the active ingredient(s). In addition, an extremely rapid release rate could overwhelm the absorption process and result in swallowing of significant amounts of active ingredient(s), possibly producing gastric distress.

A preferred release profile of appetite suppressant active from the carrier is in the range of 10-60% percent by weight ("PBW") of the total content of active within the first 10 minutes of placement into the oral cavity, more preferably at least about 25% PBW of the total content of active within the first 5 minutes. The initial rapid release of active is followed by slower release of the remaining active over an additional period of 10-60 minutes, preferably at least about 20 minutes, that the delivery system remains in the mouth. The overall release pattern provided by this formulation is considered a form of sustained release delivery system, wherein a continued release of active over a sustained period of time keeps the active concentration in the bloodstream at or near a pharmacologically effective concentration. Thus, sustained release assures relief from

cravings or other discomforts. The two doses help to prevent a relapse, a situation frequently encountered where cravings, etc. are environmentally induced.

The pattern of release of buffer chemicals likewise is important to the invention, because of the need to control oral pH. Many active ingredient components of medicaments that may be incorporated into the delivery system are sensitive to pH conditions. Medicaments that contain basic nitrogen moieties in their structure may demonstrate a pKa in the range of 3 to 11. Under acidic pH conditions in the mouth (pH 6.0 to pH 7.0), many of the useful compounds would be highly ionized and would not be efficiently absorbed into the bloodstream by the transmucosal route. Buffer chemicals such as alkali carbonates rapidly elevate the pH of saliva in the mouth, and provide favorable pH conditions for efficient absorption of active ingredients.

Buffering agents are those compounds that assist in release and conversion of an active from an ionized state ("ionized active") to an unionized state ("unionized active"). Passage of actives across the mucous membranes inside the mouth to the bloodstream is due primarily to passive diffusion of unionized active. Upon release from the carrier into the mouth, some active ingredients will be highly ionized as a result of pH characteristics or oral fluids, while others will be primarily neutral or unionized. The unionized form of active is absorbed through the oral mucosa. As the buffer is also released, and dissolves in the mouth with the active, the pH in the oral cavity may be controlled. To be effective, the buffer material should be released in sufficient amounts with the release of the active to create a basic or alkaline pH environment inside the mouth, thereby unionizing the active and facilitating effective delivery of the active. Consequently, conversion of the active from ionized to unionized in mouth saliva is an important step in providing

adequate blood levels of the appetite suppressant active. Buffer compounds assist with this conversion by raising the pH and thereby facilitating absorption of the medicament.

For example, use of potassium carbonate buffer in the delivery vehicle alters the mouth pH conditions to approximately 7-10 and provides a suitable environment for efficient absorption of most active ingredients containing basic nitrogen groups. Any one or combination of nontoxic potassium, sodium, calcium, magnesium or aluminum salts may be used to elevate mouth pH conditions. Examples of such chemicals are potassium carbonate, potassium bicarbonate, sodium carbonate, sodium bicarbonate, potassium citrate, sodium citrate, calcium phosphate, magnesium hydroxide, magnesium carbonate, magnesium trisilicate, aluminum carbonate and aluminum hydroxide. The buffer preferably comprises about 0.1 to 10% of the total delivery system composition, and desirably will be within the range of about 0.5 to 5% thereof.

Table 1 demonstrates the dose of various appetite suppressant actives suitable for absorption through the buccal mucosa within the first 5 minutes after oral administration when oral pH is raised to 9, as well as the percentage of each active that would be absorbed.

| Mendicant | Oral Dosage | pKa | % buccal absorption at pH = 9 | Buccally absorbed in first 5 min with 25% release | Half-life |
|---|---|---|---|---|---|
| d-amphetamine | 5-15 mg | 9.9 | 29 | 0.4-2.2 mg | 7.0-34.0 hr |
| l-amphetamine | 15-60 mg | 9.9 | 29 | 1.1-8.7 mg | 7.0-34.0 hr |
| Ephedrine | 12.5-50 mg | 9.6 | 35 | 1.1-8.8 mg | 5.0-7.5 hr |
| Pseudoephedrine | 30-60 mg | 9.7 | 33 | 2.5-9.9 mg | 3.0-16.0 hr |
| d-methamphetamine | 2.5-15 mg | 9.9 | 29 | 0.2-2.2 mg | 6.0-15.0 hr |
| l-methamphetamine | 2.5-60 mg | 9.9 | 29 | 0.2-8.7 mg | 6.0-15.0 hr |
| Phenylpropanolamine | 25-75 mg | 9.1 | 48 | 3.0-18.0 mg | 3.0-4.4 hr |
| Propylhexadrine | 1-25 mg | 10.4 | 20 | 0.1-2.5 mg | - |
| Phentermine | 30 mg | 10.1 | 25 | 1.9 mg | 19-24 hr |
| Phendimetrazine | 35 mg | 7.6 | 80 | 7.0 mg | - |
| Sibutramine | 5-15 mg | - | - | - | 3.6 hr |

The relatively long half-lives of the medicaments listed in Table 1 provide sustained symptom relief for several hours after the product has been removed from the mouth or completely dissolved.

The pattern of release may vary as desired, and depending on the specific active used in the composition. Therefore, some compositions may desirably deliver about 60% of their active content within 10 minutes of oral manipulation, and up to about 90%, more preferably 100%, of their active content within about 50 minutes, more desirably within about 30 minutes. In this way, a prolonged loaded concentration of the appetite

suppressant active is maintained in the blood for at least about 20 minutes, more preferably about 30 minutes, and even more desirably about 60 minutes after use begins.

In one embodiment of the invention, it is preferable that the buffer be chosen so as to yield a pH in excess of at least about 7.5 inside the mouth, and even more desirably in excess of about 8.0, or even greater than about 8.5. A pH level of at least about 9.0 is particularly preferred inside the mouth after about 10 minutes, more preferably after about 5 minutes from the onset of mastication or manipulation. Even more desirable is a pH of at least about 9.0 after about 3 minutes, and especially after about 1 minute. The buffer system is preferably optimized in conjunction with the other components of the formulation so that it does not result in excessive release of active inside the mouth, which may overwhelm the user. The quantity and type of buffer materials furthermore should not cause unpleasant organoleptic side effects, such as irritation, coughing or choking, etc.

Following the initial release of buffer in the first 5-10 minutes or so (i.e. the first dose), there is continued release of buffer at a slower rate (i.e. the second dose). Initial pH of mouth saliva peaks in a range of about 7.5 to 9.5 and thereafter drops back toward basal pH levels as the buffer in the carrier is slowly exhausted. As the pH of mouth saliva drops, the fraction of active compound in mouth saliva that is converted to an absorbable form drops proportionately. Thus, the amount of active absorbed during this phase is primarily dependent upon mouth saliva pH. After about 10 minutes or so of chewing and/or manipulation, although mouth saliva pH begins to fall because of smaller amounts of buffer release from the gum, there is increased carbonate buffer produced naturally from the stimulation of continued chewing. Consequently, absorption of active

continues to be enhanced from increased pH effects caused by the chewing and/or manipulation action of the carrier.

The carrier of a composition containing medicament may be a chewing gum. One benefit of using chewing gum as the carrier is the potential for lower abuse liability of formulations containing potentially abusable drugs as the active (e.g., amphetamine, methamphetamine). Specifically, substantial effort would be required to remove the active from the gum matrix for intravenous administration or abuse of the product. This benefit also would be applicable to lozenge formulations, though to a slightly lesser degree.

The gum matrix is preferably comprised of a chewing gum base having hydrophobic and relatively hydrophilic components, a water soluble portion that preferably includes sweeteners and an active(s), fillers that may be insoluble or partially water soluble, and water insoluble flavorants and colorants. In addition, water-soluble buffer chemicals are added to control the pH conditions in the mouth. In some cases, it may be desirable to include an antioxidant to protect the gum base, flavorants and active ingredients from oxidation.

The initial rapid release of medicament and buffer chemicals in the oral cavity from gum-based formulations occurs through the chewing action and saliva dissolution of ingredients. The water-soluble components begin to dissolve upon initiation of chewing due to the wetting action of saliva in the mouth. The insoluble materials of chewing gum (gum base, fillers, flavorants) primarily are retained in the mouth throughout the chewing period. Portions of water-soluble medicament and buffer remain embedded in the gum. In addition, a portion of the soluble active ingredient(s) may be reabsorbed into the gum

base. After the initial rapid release of water soluble active ingredient(s) and buffer occurs, slower release of the remaining portion of water soluble active ingredient(s) and active ingredient(s) reabsorbed by the gum base occurs upon further chewing. The user can regulate the release of the soluble materials, including release of the active ingredient, by adjusting the rate of chewing.

One or more gum base materials that are at least partially hydrophilic in nature are especially desirable. It is even more preferred that the material have significant hydrophilic characteristics. Of these types of material, polyvinyl acetate is particularly preferred. Especially preferred is low to medium weight polyvinyl acetate, such as polyvinyl acetate having a molecular weight (MW) of about 12,000 to 45,000. In an especially desirable embodiment of the invention, the amount of polyvinyl acetate (PVA) in the gum base is maximized, and the quantity of non-PVA polymers such as butadiene-styrene, butylene-based polymers and copolymers is preferably minimized. Because polyvinyl acetate tends to be relatively hydrophilic in nature, it may allow for better release of the saliva-soluble ingredients from the gum composition. The gum base matrix may comprise from about 40 to 90% by weight of the total composition of the invention, preferably less than about 70% by weight, more preferably about 50 to 60% by weight of the total composition.

The gum base matrix may additionally contain other ingredients well known in the art and selected from the group consisting of plasticizers and softeners to help reduce the viscosity of the gum base to a desirable consistency and to improve the overall texture and bite. These compounds are also noted for their emulsifying properties. As non-limiting examples, compounds such as lecithin, mono- and diglycerides, lanolin, stearic

acid, sodium stearate, potassium stearate, glycerol triacetate, glycerol monostearate and glycerin are provided. Stearic acid, lecithin and mono- and diglycerides are particularly preferred. Plasticizers and softeners are desirable as part of the formulation because in addition to softening the primary gum base polymeric compound, they also seem to facilitate release of the active upon mastication. When added, the plasticizers and softeners will comprise from about 0.1 to 20% of the gum base matrix formulation, and more desirably will be within the range of about 5-15% thereof.

The gum base matrix may also comprise both natural and synthetic hydrophobic elastomers and rubbers, natural and synthetic resins, fats, oils, waxes, and inorganic fillers. The elastomers and resins may be selected from the many gum base materials known in the art including naturally-derived products such as chicle, julutong, and gutta percha and synthetic materials such as butyl rubber, polyisobutylene, isobutylene, butadiene-styrene copolymers, polyethylene, polyvinylesters such as polyvinyl acetate, and mixtures of any of the foregoing.

Other materials which may be included as part of the gum base matrix include elastomer solvents. These are typically selected from the group consisting of rosin and resin material typically utilized in the confectionery chewing gum industry. Examples include methyl, glycerol, and pentaerythritol esters of rosins or modified rosins, such as hydrogenated, dimerized or polymerized rosins or mixtures thereof. More specific examples include pentaerythritol ester of partially hydrogenated wood rosin, pentaerythritol ester of wood rosin, glycerol ester of wood rosin, glycerol ester of partially dimerized rosin, glycerol ester of polymerized rosin, glycerol ester of tall oil rosin, glycerol ester of wood rosin and partially hydrogenated wood rosin and partially

hydrogenated methyl ester of rosin, such as polymers of alpha-pinene or beta-pinene, and terpene resins including polyterpene and mixtures thereof. Elastomer solvents can comprise from about zero to 75% of the gum base. It is preferable, however, to minimize or even eliminate the quantity of rosin/resin in the gum base. It is especially desirable not to exceed about 10% by weight of the gum base matrix with rosin/resin compound(s).

Filler material may be selected to enhance the chewability of the final chewing gum composition. In at least some embodiments, certain filler material may also enhance the release and absorption of nicotine and other tobacco alkaloids. Those fillers which are substantially non-reactive with other components of the final formulation are also preferred. Desirable filler materials will therefore include calcium carbonate, magnesium silicate (talc), as well as dicalcium phosphate, and any mixtures thereof. Particularly preferred may be dicalcium phosphate. Other metallic mineral salts may also be utilized as filler material, as for example alumina, aluminum hydroxide, and aluminum silicates, provided they possess the characteristics heretofore set forth. Filler material will typically comprise about 0.1 to 30% of the gum base matrix, and more preferably will be within the range of about 10 to 20% thereof.

Trace amounts of standard industry preservatives such as butylated hydroxy toluene (BHT) may also be present in amounts less than about 0.1% or so of the gum base.

Such ingredients are well known in the art and are selected to adjust the gum base consistency to a desirable consistency for overall gum texture and chewability. In one embodiment, it is highly preferable that the gum base be constructed to provide an initial soft chew that continues to be relatively soft-chewing throughout 30 to 45 minutes of

chewing. The characteristics of a soft-chewing gum base facilitate the ability of the individual chewer to exert control over the amount and speed of release of active ingredient(s) during the chewing period. An additional desirable feature of the gum base is the ability to release reliably a portion of the active ingredient(s) during the early stages of chewing. Preferably, the gum base allows release of 10-60% of the initial dose of active ingredient(s) within the first 10 minutes of chewing. The composition in all its embodiments can be soft and pliable inside the mouth, both upon initial chew and after prolonged mastication.

It is preferable that the formulation be substantially non-liquid as well. That is, the formulation of the invention is substantially 0% liquid. Typically, chewing gum formulations comprise three major components. These are gum base, solids and liquids. By excluding substantially all liquid from the formulation, incompatibility problems between the various components, and the concomitant problems of instability (especially of the active materials), migration and interaction among the actives, flavors, sweeteners and buffers, etc, can often be avoided.

The bulk sweeteners may constitute about 20-80% by weight of the chewing gum and are preferably sugarless sweeteners. Such ingredients are well known in the art and are selected to impart improved palatability to the chewing gum and to aid in masking the bitter or unpleasant taste of some actives and/or dietary supplements. In addition, flavorants may be used in the chewing gum within the range of 0.1-10% by weight, preferably between about 0.5-4% by weight of the chewing gum. The flavoring agents may include natural and synthetic agents and all such combinations thereof. Colorants may include food and pharmaceutical grade coloring agents.

Other possible physical embodiments of the chewing gum composition of the invention include, for example, various centerfill configurations. In these embodiments the gum base matrix will at least partially surround a centerfill. The centerfill will contain one or more of the active substances. The centerfill may be a liquid or semi-liquid material and preferably will be low fat or fat free. In addition to the active(s), the centerfill may contain one or more sweeteners and/or flavorants as heretofore described. A combination of saccharide material, flavoring, polyol and edible gel material is one example of a centerfill. One or more of the active ingredient(s) and/or the sweeteners and flavorants, etc. may be encapsulated as previously set forth, and then incorporated into the centerfill.

The centerfill embodiment may be particularly desirable wherein immediate release of the active is particularly desired (i.e. less than 1 minute). Encapsulating the active(s) in this embodiment may help to taste-mask those actives which provide an undesirable organoleptic sensation. Other than the centerfill portion, it is preferred that the formulation ingredients of this embodiment be substantially liquid-free, or about 0% liquid.

Alternatively, the carrier may be a lozenge or candy. A wide variety of lozenges and candies may be used as the multi-phasic drug delivery vehicle for medicament and buffer chemicals. Lozenges and candies are flavored dosage delivery systems for medicament(s) and dietary supplements that are held in the mouth, wetted with saliva and sucked until dissolution occurs in a multi-phasic manner. Generally, lozenges and candies have a base composed of a mixture of sugar and other carbohydrate bulking agents. Non-fermentable sugars such as sorbitol, mannitol, xylitol, isomalt and

hydrogenated starch hydrolysates may also be used. A general discussion of lozenges and tablet forms of confectionery may be found in H.A. Lieberman, Pharmaceutical Dosage Forms, Volume 1: Tablets (1989), Marcel Dekker, Inc., New York, N.Y. at Medicated Confections, pages 419-582, which disclosure is incorporated herein by reference.

Alternatively, the carrier may be a tablet. Tablets are dosage delivery systems for medicament that is placed in the mouth or under the tongue for multi-phasic dissolution of the active and absorption through epithelial tissues. A general discussion of tablet forms may be found in H.A. Lieberman, Pharmaceutical Dosage Forms, Volume 1: Tablets (1989), Marcel Dekker, Inc., New York, N.Y. at Medicated Confections, pages 75-418, which disclosure is incorporated herein by reference.

A wide array of changes and modifications to the embodiments of the invention described above will be apparent to persons skilled in the art. While this invention has been described as having a preferred embodiment, it is understood that the invention is not limited to the described features. To the contrary, the invention is capable of further modifications, uses, and/or adaptations following the general principles of the invention and therefore includes such departures from the present disclosure as come within the known or customary practice in the art to which the invention pertains, and as may be applied to the central features set forth above, and which fall within the scope of the appended claims and their equivalents.

**We claim as follows:**

1. A composition for oral administration of an active for appetite suppression, comprising:

a carrier selected from the group consisting of gums, lozenges, candies and tablets suitable for administration in an oral cavity;

an active for appetite suppression; and

a water-soluble buffer facilitating bi-phasic release of said active for appetite suppression for transmucosal absorption within the oral cavity of a user.

2. The composition of claim 1, wherein said buffer facilitates a first release of at least about 25% by weight of said active within about 5 minutes after oral administration.

3. The composition of claim 2, wherein said buffer facilitates a second release for a total of at least about 90% by weight of said active within about 50 minutes after oral administration.

4. The composition of claim 1, wherein said active is selected from the group consisting of d-amphetamine, l-amphetamine, mixtures of d- and l- amphetamine, ephedrine, pseudoephedrine, d-methamphetamine, l-methamphetamine, mixtures of d- and l- methamphetamine, phenylpropanolamine, propylhexadrine, phenylethylamine derivatives, phentermine, phendimetrazine, and sibutramine.

5. The composition of claim 1, wherein said buffer is selected from the group consisting of potassium carbonate, potassium bicarbonate, sodium carbonate, sodium bicarbonate, potassium citrate, sodium citrate, calcium phosphate, magnesium hydroxide, magnesium carbonate, magnesium trisilicate, aluminum carbonate, and aluminum hydroxide.

6. The composition of claim 5, wherein said buffer achieves a predetermined pH within the oral cavity within about 5 minutes after oral administration.

7. The composition of claim 6, wherein the predetermined pH is between about 7 to about 10.

8. The composition of claim 6, wherein at least a portion of said active is unionized at the predetermined pH for transmucosal absorption.

9. The composition of claim 1, wherein said carrier and said buffer rapidly achieve a pharmacologically effective concentration of said active for appetite suppression in the bloodstream of a user within about 5 minutes after oral administration and maintain the concentration of said active for appetite suppression in the bloodstream at or near the pharmacologically effective concentration for at least 20 minutes after oral administration.

10. The composition of claim 1, wherein said carrier is a chewing gum including at least one substantially hydrophilic polymer and at least one hydrophobic polymer.

11. The composition of claim 1, wherein said active for appetite suppression comprises between about 0.01 to about 10% by weight of said composition.

12. The composition of claim 1, further comprising at least one additional ingredient selected from the group consisting of plasticizers, softeners, elastomer solvents, fillers, and sweeteners.

13. A method of delivering a medicament for appetite suppression in a bi-phasic manner, comprising the steps of:

providing a carrier having an active for appetite suppression and a buffer, the carrier suitable for oral administration;

placing the carrier into the mouth of a user and releasing a first, rapid pharmacologically effective dose of the active in an oral cavity for a first period of time; and

thereafter releasing a second, prolonged pharmacologically sufficient dose of the active in the oral cavity for a second period of time longer than the first period of time.

14. The method of claim 13, including the step of releasing at least about 25% by weight of the active during said releasing the first, rapid initial pharmacologically effective dose step.

15. The method of claim 14, wherein the first period of time is 10 minutes or less during said releasing a first, rapid initial pharmacologically effective dose step.

16. The method of claim 15, wherein the second period of time is 30 minutes or more during said releasing a second, prolonged pharmacologically sufficient dose step.

17. The method of claim 13, including the step of releasing at least about 90% by weight of the active within about 50 minutes during said releasing steps.

18. The method of claim 13, including the step of regulating pH in the oral cavity using a sufficient amount of buffer for facilitating transmucosal absorption in the oral cavity during said releasing steps.

19. The method of claim 13, including the step of providing a buffer selected from the group consisting of potassium carbonate, potassium bicarbonate, sodium carbonate, sodium bicarbonate, potassium citrate, sodium citrate, calcium phosphate, magnesium hydroxide, magnesium carbonate, magnesium trisilicate, aluminum carbonate, and aluminum hydroxide.

20. The method of claim 13, including the step of providing an appetite suppression constituent selected from the group consisting of d-amphetamine, l-amphetamine, mixtures of d- and l- amphetamine, ephedrine, pseudoephedrine, d-methamphetamine, l-methamphetamine, mixtures of d- and l- methamphetamine, phenylpropanolamine, propylhexadrine, phenylethylamine derivatives, phentermine, phendimetrazine, and sibutramine.

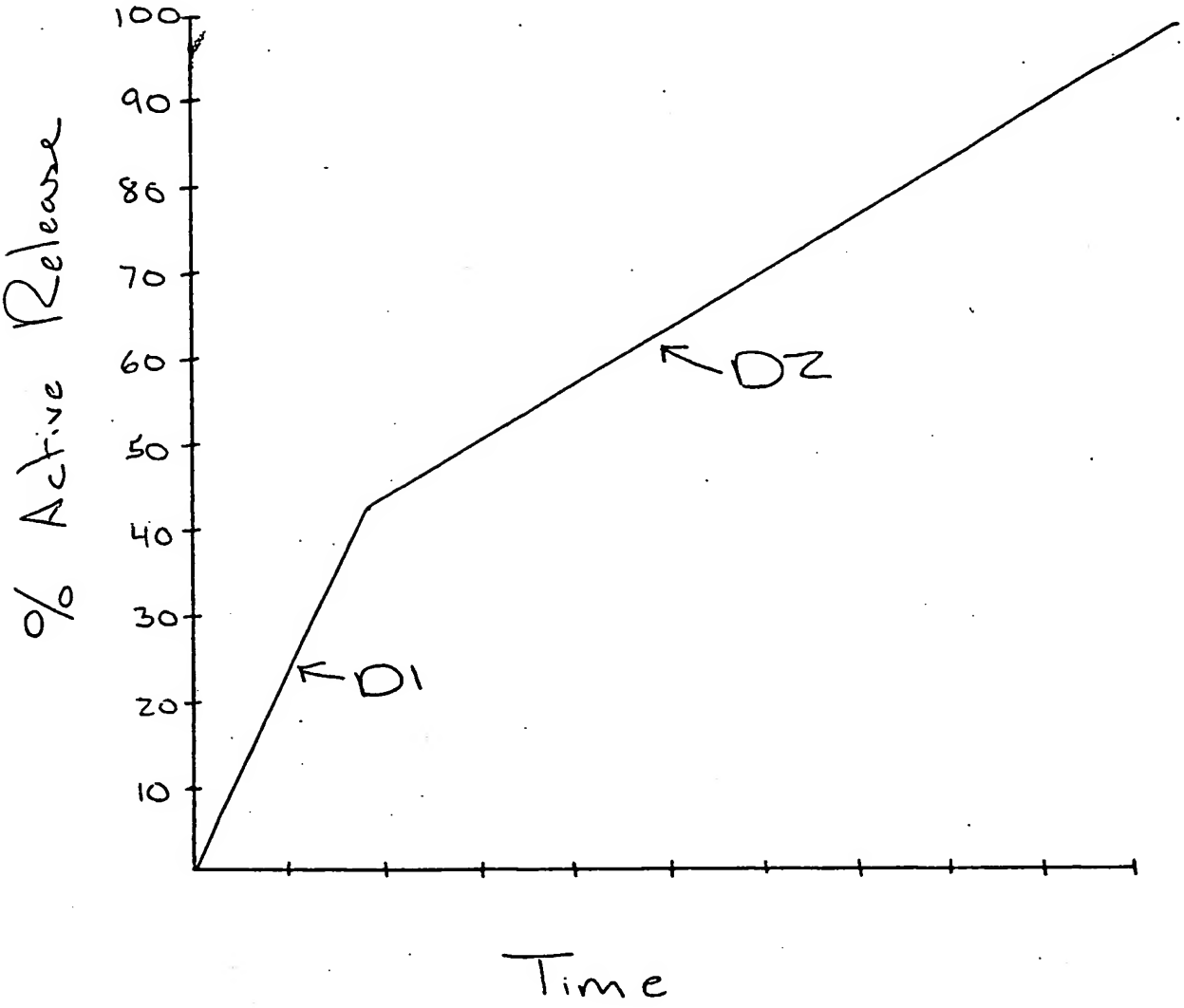


Fig. 1

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/13101

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 9/22
US CL : 424/468, 484, 485, 488
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/468, 484, 485, 488

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 5,472,711 A (BAICHWAL) 05 December 1995 (05.12.1995), abstract, column 5 through column 10, column 16 through column 18. | 1-20 |
| Y | Database HCAPLUS on STN, AN:2001:868177, PINNEY et al, 'Chewing gums, lozenges, candies, tablets, liquids, and sprays for efficient delivery of medications and dietary supplements, WO 2001089476, 2001, see Abstract. | 1-20 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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